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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,336	JOLIVET ET AL.	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-15, and 17-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 5/14/07, in response to the Office action (mailed 12/19/06), have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

This rejection is made final.

Status of the Claims

Claims 1, 3-15, and 17-60 are currently pending in this application.

Response to Applicant's arguments

Obviousness-Type Double Patenting Rejection (claims 1, 3-15, and 17-60)

Applicant contends the following (see applicant's Response filed 5/14/07, pages 11-14; hereafter referred to as Response):

1) None of the reference claims of Gourdeau '480 (i.e. US Patent 6,630,480) recite the limitation "administration by continuous infusion, let alone continuous infusion for at least 72 hours. Applicant states that the "only description of administration recited in the claims is the administration of effective amounts (claims 1 and 21) and specific amount ranges and dosages."

2) It is unnecessary in this case to use the specification to define "effective amount" because reference the claims (of Gourdeau '480) provide information for one skilled in the art to interpret effective amounts; even if it were permissible to refer to the specification to define effective amounts, one does not need to refer to the disclosure on modes of administration to determine effective amounts.

3) Gourdeau '480 is not effective prior art for obviousness determinations under 35 USC 103(a) because it is a divisional of Gourdeau '036 and both Gourdeau '036 and '048 were commonly assigned at the time the invention of the instant application was made. Also, Gourdeau '639 is ineffective prior art for the same reason because it was also commonly assigned at the time the invention of the instant application was made.

4) Chu et al. (US '667) does not teach administering troxacitabine or a pharmaceutically acceptable salt thereof by infusion.

5) De Bono et al. (abstract) as argued by the examiner teaches administering troxacitabine as a daily 30 minute infusion for five days every 3 to 4 weeks. However, this reference does not provide any rationale that would lead one of ordinary skill in the art to select an administration regime in which a patient would be administered troxacitabine by continuous infusion for a period of at least 72 hours.

6) The above traversal arguments (#1-5) are also proffered by applicant in response to the provisional obviousness-type double patenting (ODP) rejection based on copending applications 10/824,563, 10/107,795 (now abandoned), 10/826,960 (now US Patent 6,645,972).

In response, applicant's argument in connection with the ODP involving abandoned application 10/107,795, is found to be persuasive. The provisional ODP rejection with respect to application 10/107,795 is hereby withdrawn.

Applicant's argument identified under above item #6, regarding the fact that application 10/826,960 is now issued patent 6,645,972 is found to be persuasive. Thus, the ODP rejection in connection with application 10/826,960 is also withdrawn.

Applicant's above arguments identified under items #1-3 are found to be persuasive. The rejections based on said references are withdrawn.

Applicant's above arguments identified under items # 4-5 are not found to be persuasive for the following reasons:

i) Applicant's conclusory statement that there is no specific suggestion or teaching in the references to combine prior art is not found to be persuasive as KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness (See the recent Board decision Ex parte Smith, -- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 1007, citing KSR, 82 USPQ2d at 1396).

ii) Applicant's individual arguments against the cited references is not found to be persuasive as one cannot show nonobviousness by attacking the references individually where the rejections are based on combinations of references i.e. the references must be viewed as whole. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, each reference does not need to teach all the elements in a claim, but as combined the references must teach and/or suggest each limitation. In this case, the combined references teach and/or suggest each claimed limitation.

iii) Although there is some merit to applicant's contentions that there is a significant difference between the 30-minute duration of administration of the intravenous infusion of troxacitabine as taught by De Bono et al. (J. Clin. Oncol. 2002;2091):96-109, abstract only) as compared with the instantly claimed at least 72 hours infusion time (i.e. argument #1), and the use of the specification as a dictionary in connection with the ODP rejection involving Gourdeau '480 (argument #2), these factors are not sufficient to overcome the rejections as someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention by optimizing (infusion time, drug plasma levels, duration of therapy etc.) with reasonable predictability for the reasons previously made of record in the Office action mailed 12/19/06, and as evidenced by the teaching of Lokich et al. (Lokich et al. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25). Besides, it is within the knowledge and skill of an artisan skilled in the art to conduct routine experimentation to determine the therapeutically effective amount of a drug, and/or the optimal duration of infusion, and/or the optimal drug plasma/serum concentration.

Lokich et al. teach that some anti-neoplastic agents are administered as a continuous 24-hours infusion for five or more days routinely, such as 5-fluorouracil and cladrabine, while some agents, for example, fludarabine and etoposide are administered as a daily bolus for three to five days. Lokich et al. teach that the rationale for infusional administration for chemotherapeutic agents is generally based upon observing schedule dependency in experimental systems and drug pharmacology in

which a short plasma half-life following bolus administration would limit tumor cell exposure; the infusion schedule may also mitigate the acute and chronic toxicities commonly associated with high peak levels (page 15, col. 1, introduction section, lines 8-15; see also page 18, Table 3). Lokich et al. teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3). Lokich et al. also teach that the selection of a duration of infusion is often arbitrary or based on achieving specific objectives such as decreasing allergic, gastrointestinal or other adverse effects; the dose intensity (DI) and the maximum tolerated dose (MTD) for infusional schedules may be different from those achieved with bolus administration and as such may influence the clinical effectiveness of the therapy (page 15, col. 2, lines 3-10). Instant claims 1, 8, 13, recites the term "continous infusion for a period of at least 72 hours;" instant calim 23 recites the term "continuous infusion is administered for a period of 3 to 7 days;" claim 24 recites the term "continuous infusion for a period of 3 days; claim 25 recites the term "continuous infusion is administered for a period of 4 days;" claim 26 recites the term "continuous infusion is administered for a period of 5 days; claim 27 recites the term "continuous infusion is administered for a period of 6 days; claim 28 recites the term "continuous infusion is administered for a period of 7 days.' Lokich et al. teach that an important component to infusional chemotherapy is not only the MTD but the actual duration of infusion which influences the MTD (page 23, lines 1-3). For some agents, cumulative effects with infusional administration may result in accentuated toxicity

necessitating treatment interruptions, but for most drugs, adjustments in the dose rate will permit long term administration for weeks or even months (page 23, lines 3-8). Instant claim 33 recites the term "continuous infusion at an interval of every 4 weeks; claim 34 recites the term "continuous infusion at an interval of every 3 weeks; claim 35 recites the term "continuous infusion at an interval of every 5 weeks. Further, Lokich et al. teach that the role of treatment duration in terms of therapeutic advantage has not been unequivocably established for any agent but conceptually, the longer duration permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction ...(page 23, col. 1, lines 8-18).

Rejection under 35 USC 112, second paragraph (claims 1, 3-15, and 17-60)

Applicant contend the following (Response, page 15):

7) the limitation "effective amount" is not indefinite because claims 1, 8, and 13 all expressly recite methods "for the treatment of cancer within a patient." One of skill in the art upon reading the claim language in its entirety would recognize that the effective amounts are amounts effective for the treatment of cancer.

8) claims 4, 18, and 19 are not indefinite since one of ordinary skill in the art would still recognize that the claims recite that the patient had acute myelogenous leukemia, chronic myelogenous leukemia ...etc (see applicant's Response filed 5/14/07).

This rejection is withdraw as applicant's arguments identified above as items # 7-8 are found to be persuasive.

Rejection under 103(a) (claims 1, 3-15, 17-60)

Applicant asserts the following (Response, pages 15-17):

9) De Bono abstract describes a Phase I study wherein patients were administered troxacitabine "as a 30-minute IV infusion daily for 5 days," while the instant claims recite the limitation "continuous infusion for a period of at least 72 hours."

10) Examiner fails to explain how the reference language "a 30-minute IV infusion daily for 5 days" could be construed by one of ordinary skill in the art to mean a continuous infusion over a period of at least 72 hours. The examiner's argument regarding half-lives for drug elimination merely refers to an asserted "continuous" amount of drug in the bloodstream. This argument does not provide any reason why one would interpret 30 minutes to be the same as at least 72 hours.

11) Chu et al. (US '667) provides no rationale for modifying the disclosure of De Bono in such a manner as to arrive at applicant's claimed dosage range because it fails to mention the limitations "infusion," or "continuous infusion", let alone 'continuous infusion for at least 72 hours. "

12) The examiner's argument suggesting that it is possible to manipulate infusion rate to achieve or maintain certain concentrations of a drug is at best an assertion of obvious to try, which is impermissible rationale for obviousness under 103(a).

13) Applicant request withdrawal of the rejections under 35 USC 102(a) and 35 USC 103 for the reasons discussed above (page 16, lines 1-2). It is noted that applicant's reference to rejections under 35 USC 102(a) is being disregarded as no 102(a) rejections were made in the previous action.

In response, applicant's arguments identified as items #9-13 are not found to be persuasive for the reasons stated below:

i) Applicant's argument that there is no specific suggestion or teaching in the references to combine prior art is not found to be persuasive as KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness (See the recent Board decision Ex parte Smith, -- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 1007, citing KSR, 82 USPQ2d at 1396).

ii) Applicant's individual arguments against the cited references is not found to be persuasive because one cannot show nonobviousness by attacking the references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); each reference does not need to teach all the elements in a claim, but as combined the references must teach and/or suggest each limitation. In this case, the combined references teach and/or suggest each claimed limitation.

iii) Although there is some merit to applicant's contentions that there is a significant difference between the 30-minute duration of administration of the intravenous infusion of troxacitabine as taught by De Bono et al. (J. Clin. Oncol. 2002;2091):96-109, abstract only) as compared with the instantly claimed at least 72

hours infusion time (i.e. arguments #9-10; see also applicant's Response, pages 15-17), this is not sufficient to overcome the rejection as someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability for the reasons previously made of record in the Office action mailed 12/19/06, and as evidenced by the teaching of Lokich et al. (Lokich et al. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25). Besides, it is within the knowledge and skill of an artisan skilled in the art to conduct routine experimentation to determine the therapeutically effective amount of a drug, and/or the optimal duration of infusion, and/or the optimal drug plasma/serum concentration.

Lokich et al. teach that some anti-neoplastic agents are administered as a continuous 24-hours infusion for five or more days routinely, such as 5-fluorouracil and cladrabine, while some agents, for example, fludarabine and etoposide are administered as a daily bolus for three to five days. Lokich et al. teach that the rationale for infusional administration for chemotherapeutic agents is generally based upon observing schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life following bolus administration would limit tumor cell exposure; the infusion schedule may also mitigate the acute and chronic toxicities commonly associated with high peak levels (page 15, col. 1, introduction section, lines 8-15; see also page 18, Table 3). Lokich et al. teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or

longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3). Lokich et al. also teach that the selection of a duration of infusion is often arbitrary or based on achieving specific objectives such as decreasing allergic, gastrointestinal or other adverse effects; the dose intensity (DI) and the maximum tolerated dose (MTD) for infusional schedules may be different from those achieved with bolus administration and as such may influence the clinical effectiveness of the therapy (page 15, col. 2, lines 3-10). Lokich et al. teach that an important component to infusional chemotherapy is not only the MTD but the actual duration of infusion which influences the MTD (page 23, lines 1-3). For some agents, cumulative effects with infusional administration may result in accentuated toxicity necessitating treatment interruptions, but for most drugs, adjustments in the dose rate will permit long term administration for weeks or even months (page 23, lines 3-8). Further, Lokich et al. teach that the role of treatment duration in terms of therapeutic advantage has not been unequivocably established for any agent but conceptually, the longer duration permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction ...(page 23, col. 1, lines 8-18).

The below discussion of the 103(a) rejection is also incorporated by reference.

The rejection

Summary of Rejections

Claims 1, 3-15, and 17-60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 9, 10, 14,15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 30, 31, 32, 33, 34, 35, and 36 of U.S. Patent

6,630,480 (Gourdeau '480), in view of U.S. Patent 6,747,036 (Gourdeau '036), in view of U.S. Patent 6,800,639 (Giles '639), and further in view of U.S. Patent 5,817,667 (Chu '667), and further in view of De Bono et al.

Claims 1, 3-15, and 17-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the following: claims 11-21 of copending Application No. 10/824,563 in view of Gordeau '480, in view of Gordeau '036, in view of Giles '639, in view of Chu '667, and further in view of De Bono et al.

Claims 1, 3-15, and 17-60 are rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Chu et al. (US patent 5,817,667), and further in view of Benet LZ et al. (Benet et al. Pharmacokietics: The dynamics of drug absorption, distribution, and elimination. In, Goodman & Gilmans: The Pharmacological Basis of Therapeutics, 9th edition (1996): pages 3 and 18).

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-15, and 17-60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 9, 10, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 30, 31, 32, 33, 34, 35, and 36 of U.S. Patent 6,630,480 (Gourdeau '480), in view of U.S. Patent 6,747,036 (Gourdeau '036), in view of U.S. Patent 6,800,639 (Giles '639), and further in view of U.S. Patent 5,817,667 (Chu '667), and further in view of De Bono et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

In particular, claim 1 of Gordeau '480 recites a method for treating a patient with leukemia comprising administering to said patient having chronic myelogenous leukemia or acute myelogenous leukemia, a therapeutically effective amount of a compound having "formula I." Unlike the claims of the instant application (i.e. claims 1, 3-15, and 17-60), the method of said reference claim 1 does not disclose the limitations of a continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0 μM is achieved during the administration. Specifically, the method of claim 1 of the reference is a one-step method for treating a patient with leukemia comprising administering a therapeutically effective amount of troxacitabine. Although claim 1 of Gordeau '480 does not recite a specific mode for administering the desired therapeutically effective amount of troxacitabine to a patient, or a specific period of time for administering the desired therapeutically effective amount of troxacitabine to a patient, or the specific steady state plasma concentration of troxacitabine to be achieved during the administration of troxacitabine to a patient, someone of ordinary skill in the art would reasonably conclude that it is necessary for troxacitabine to be administered to a patient via a particular mode, for a particular period of time, which would necessarily achieve a particular steady state plasma concentration of troxacitabine during the administration of the drug, in order to deliver the desired therapeutically effective amount of troxacitabine to a patient, these limitations are construed to be within the skill and knowledge of an artisan skilled in the art for the reasons evidenced by Lokich et al. (Lokich et al. Dose intensity for bolus versus infusion

chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25).

The above discussion in connection with the Response to Arguments involving the ODP rejections is incorporated by reference.

As stated in the Office action mailed 12/19/06 (see pages 2-8), Gordeau '036 teaches a method of treating leukemia comprising administering synergistic combinations of troxacitabine and doxorubicin (i.e. reference claims 1 and 11) and said combinations further comprising administering a multidrug resistance reversing agent or a biological response modifier (i.e. reference claims 4 and 5), or a biological response modifier (i.e. reference claims 6, 7, and 8). Gordeau '036 also teaches the sequential administering of troxacitabine and doxorubicin (.i.e. reference claim 9) and the simultaneous administering of troxacitabine and doxorubicin (.i.e. reference claim 10).

Giles '639 teaches a method of treating a patient having pancreatic cancer comprising administering a therapeutically effective amount of troxacitabine and gemcitabine, wherein the troxacitabine is administered at a dose of between 1 mg/m2 and 8 mg/m2 (.i.e. reference claims 17, 18, and 26).

Chu '667 teaches a method of treating cancer comprising administering to a host animal an effective amount of a compound such as troxacitabine (.i.e. reference claims 1, 2, 3, 4, 5, 6, 7, and 17). Although Chu '667 does not specifically teach renal cancer, bladder cancer, breast cancer, gastric cancer, ovarian cancer, soft tissue sarcoma, skin cancer, osteosarcoma, or rectal cancer, reference claim 1 encompasses these cancers. Further, someone of ordinary skill in the art at the time the instant application was filed

would have found it obvious to treat these tumors with the method of Gordeau '480, in view of Gordeau '036, in view of Giles '639, and in view of Chu '667.

De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only) teach the step of repeating administering troxacitabine as a 30-minute continous infusion daily for five days every 3 to 4 weeks at a dose of 1.5 and 1.2 mg/m2/day, and possibly less frequent schedules. De Bono et al. also disclose that treatment was often delayed one additional week for complete resolution of hematologic effects. Although De Bono et al. do not specifically teach the step of repeating administering troxacitabine at intervals of every 5 weeks, someone of ordinary skill in the art would have found this obvious to repeat the step of administering troxacitabine at intervals of every 5 weeks in view of De Bono et al., in view of Gordeau '480, in view of Gordeau '036, in view of Giles '639, and further in view of Chu '667.

Thus, claims 1, 3-15, and 17-60 are deemed obvious variants of the limitations of the patented subject matter claimed in Gordeau '480, in view of Gordeau '036, in view of Giles '639, in view of Chu '667, and further in view of De Bono et al., and as evidenced by the teaching of Lokich et al.

In addition, claims 1, 3-15, and 17-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the following: claims 11-21 of copending Application No. 10/824,563 in view of Gordeau '480, in view of Gordeau '036, in view of Giles '639, in view of Chu '667, and further in view of De Bono et al. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the claims are obvious variants of each other for essentially the same reasons stated above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims of the copending applications have not in fact been patented.

The above ODP rejections are maintained.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-15, and 17-60, are rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Chu et al. (US patent 5,817,667), and further in view of Benet LZ et al. (Benet et al. Pharmacokietics: The dynamics of drug absorption, distribution, and elimination. In,

Goodman & Gilmans: The Pharmacological Basis of Therapeutics, 9th edition (1996): pages 3 and 18).

The above discussion in connection with the Response to Arguments involving the 103(a) rejections is incorporated by reference.

As stated in the Office action mailed 12/19/06 (see pages 10-15), De Bono et al. teach the pharmacokinetics and pharmacodynamics of troxacitabine in thirty-nine patients with advanced solid malignancies at eight dose levels ranging from 0.12 to 1.8 mg/m2/day via a 30-min intravenous infusion for five days. De Bono et al. teach that the pharmacokinetics of troxacitabine is dose-independent wherein the mean (SD) values for the volume of distribution at steady-state and clearance (Cl) were 60 (32 L and 161 (33) ml/min, respectively, on day 1. After treatment on the fifth day, terminal half-life values averaged 39 (63) hours, and Cl, was reduced by approximately 20%, averaging 127 (27) ml/min. The principal mode of drug elimination was renal. A patient with metastatic ocular melanoma experienced a partial response. De Bono et al. further disclose that broad disease-directed evaluations of troxacitabine as a 30-minute infusion daily for 5 days every 4 weeks at a dose of 1.5 - 1.2 mg/m2/day, and possibly less frequent schedules, were warranted. Clearly, De Bono et al. teach a method for treating patients with solid malignancies, including ocular melanoma, comprising administering an effective amount of troxacitabine via a 30-min intravenous infusion for a period of 120 hours (5 days) wherein a steady state plasma concentration of troxacitabine was achieved during the administration. That a patient with melanoma experienced a partial response is evidence that the dose range from 0.12 to 1.8

mg/m2/day via a 30-min intravenous infusion for five days is a therapeutically effective amount of troxacitabine. However, De Bono et al. do not teach steady state plasma (or blood) concentration of troxacitabine of 0.03 to 2.0 μM achieved during the administration. Further, independent claims 1, 13, and 47 of the instant application recite the limitation "continuous infusion for a period of at least 72 hours." Although this limitation could be construed to mean a continuous infusion that must be infused continuously over a period of at least 72 hours, this limitation when given its broadest reasonable literal interpretation encompasses any continuous infusion, regardless of the actual infusion time, administered for a period of at least 72 hours. It is also common knowledge in the pharmacokinetic art that it requires at least four to five terminal half-lives to eliminate all of the infused drug from the body of a patient following administration of a dose of drug. Thus, the De Bono et al. once daily continuous infusion of troxacitabine intravenously infused over 30 minutes for a period of five days to provide a continuous amount of troxacitabine in the blood stream of patients with solid tumors who were administered the drug satisfies the "continuous infusion for a period of at least 72 hours" limitation recited in the claims of the instant application. As stated above, De Bono et al. do not teach steady state plasma (or blood) concentration of troxacitabine of 0.03 to 2.0 μM achieved during the administration, nor do they teach leukemia or lymphoma, but suggest further broad disease-directed evaluations of troxacitabine. Furthermore, titration of the dose, or dosing interval, or infusion duration are reasonably within the skill and knowledge of an artisan skilled in the art as evidenced by the teaching of Lokich et al. (Lokich et al. Dose intensity for bolus versus

infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25) as discussed in connection with the Response to Arguments involving the 103(a) rejections, which is incorporated by reference.

Chu et al. (US Patent 5,817,667) teach a method for treatment of cancer in humans and other host animals comprising administering an effective amount of troxacitabine (column 3, lines 21-52). Chu et al. specifically teach that various cancer cells lines are sensitive to troxacitabine, including leukemia, lymphoma, prostate, bladder, lung, colorectal, breast, pancreas, liver, ovarian cancers (see Figure 4). Chu et al. also disclose that troxacitabine is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30mM, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient. The range of steady state plasma concentration of troxacitabine recited in the instant application overlaps with the range of steady-state plasma level of troxacitaine taught by Chu et al. However, Chu et al. do not teach a "continuous infusion for a period of at least 72 hours." In view of the suggestion provided by De Bono et al., someone of skill in the art would have found it obvious to combine Chu et al. and De Bono et al. to create a method of treating patients with solid tumors and leukemia by administering a 30-minute continuous infusion of troxacitabine daily for five days to achieve steady-state plasma levels of troxacitabine of about 0.00001 – 30 mM. Chu et al. teach that humans, equines, canines, bovines and other animals, and in particular, mammals, suffering from cancer can be treated by administering

to the patient an effective amount of (-)-OddC (i.e. troxacitabine) or a pharmaceutically acceptable salt thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known anticancer or pharmaceutical agents; this treatment can also be administered in conjunction with other conventional cancer therapies, such as radiation treatment or surgery (col. 10, lines 50-59). Chu et al. teach alkylating agents (e.g. nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin); antimetablistes; nucleoside derivatives (e.g. 5-fluorouracil); nucleoside analog of dexocytidine (e.g. cytosine arabinoside); cytidine analog (e.g. 5-azacytidine); 2-fluoroadenoside-5'-phosphate (Fludarabine); anthracyclines; hormomal agents ; natural products and their derivatives; 2-chlorodeoxyadenosine(col. 2, line 7 to col. 3, line 10). Instant claims 37, 52, 56, and 59 recite, for example, nucleoside analogues as additional agents for use in combination with troxacitabine; claim 38, 53, 57, 60 recite, for example, Fludarabine as additional agents for use in combination with troxacitabine; instant claim 46 recite the term "troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations." Chu et al. do not teach

combinations of troxacitabine plus biologic modifiers as recited, for example, in claims 40 and 41; or combination of troxacitabine plus PSC 833. As evidenced by the teaching of biologic modifiers by Goodman & Gilmans' e.g. interferon-alfa; (Goodman & Gilman's, page 1227,already made of record by Examiner), and PSC 833 as taught by Ratain et al. (US Patent 5,786,344; col. 9, line 53-56; see also reference claim 17), an artisan skilled in the art would have deemed it obvious to create the instant claimed combination of troxacitabine and a biologic modifier, or a combination of troxacitabine and PSC 833, in view of Chu et al.

The limitations regarding the sequential, separate, combined, or simultaneous administration of a second agent or additional agents are reasonably construed to be within the skill and knowledged of an artisan skilled in the art. Claim 43 recites the term "at least one further therapeutic agent are administered sequentially;" claim 44 recites the term "at least one further therapeutic agent are administered simultaneously;" claim 45 recites the term "at least one further therapeutic agent are administered in separate pharmaceutical formulations;" "at least one further therapeutic agent are administered in combined pharmaceutical formulations.'

Further, Benet LZ et al. (Benet et al. Pharmacokietics: The dynamics of drug absorption, distribution, and elimination. In, Goodman & Gilmans: The Pharmacological Basis of Therapeutics, 9th edition (1996): page 18) teach that Clinical Pharmacokinetics attempts to provide both a more quantitative relationship between dose and effect and the framework with which to interpret measurements of concentration of drugs in biological fluids (page 18, column 1, lines 2-6). Benet LZ et al. further teach that the various physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so as a result of modification of pharmacokinetic parameters and that the three most important parameters are clearance, volume of distribution, and bioavailability; of lesser importance are the rates of availability and distribution of the agent (page 18, column 1, lines 10-19). In fact, someone of skill in the art can manipulate certain pharmacokinetic equations to determine the infusion rate of a particular drug to achieve or maintain steady-state concentrations of the drug within a known therapeutic range (e.g. Dosing rate (Do) = Clearance (Cl) x steady-state concentration (Css); and Cl = Dose/ total area under the curve that describes the concentration of drug in the systemic circulation as a function of time (AUC) (see page 18, columns 1-2). Thus, Benet et al. at least suggest, if not provide further motivation, to someone of skill in the art to manipulate the pharmacokinetic variables (e.g. dosing rate or infusion rate) in view of De Bono et al., and further in view of Chu et al. in order to achieve and maintain steady-state blood levels of troxacitabine of about 0.00001 – 30 mM in patients suffering from solid malignancies and leukemia wherein the troxacitabine

is administered via a continuous infusion for a period of at least 72 hours at the time the instant invention was made.

Weitman S, et al. (The new dioxolane, 9-)-2'-Deoxy-3'-oxacytidine (BCH-4556, Troxacitabine), activity against pancreatic human tumor xenografts. Clinical Cancer Research. 6:1574-1578, April 2000) is cited only to show the state of the art.

Thus, based on the suggestion of De Bono et al. that further broad disease-directed evaluations of troxacitabine are required, and the suggestion of Benet et al. that the dosing rate of a drug may be manipulated to maintain steady-state blood concentration of a drug, someone of skill in the art at the time the instant invention was made would have found it obvious to combine the teachings of De Bono et al., in view of Chu et al., and further in view of Benet et al., and as evidenced by the teaching of Lokich et al., to create the instant claimed invention with reasonable predictability.

This rejection is therefore maintained.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 8 a.m. to 4:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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23 August 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER